SACHRP Minutes, July 10-11, 2012

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Secretary's Advisory Committee on Human Research Protections (SACHRP)
Tuesday, July 10, 2012 – Wednesday, July 11, 2012
Minutes

Voting SACHRP Members Present:
Barbara Bierer (Chair), Albert J. Allen, Gary L. Chadwick, David G. Forster, Steven Joffe, Susan Krivacic, Suzanne M. Rivera, Lainie Friedman Ross, Stephen O. Sodeke

Tuesday, July 10, 2012

Welcome: Opening Remarks
Barbara Bierer, M.D., SACHRP Chair

Dr. Bierer welcomed attendees to the 29th meeting of SACHRP and reviewed the agenda. She noted that SACHRP member Carl Coleman was unable to be present, and Gary H. Gibbons is no longer able to serve on SACHRP after accepting a job as the Director of the National Heart, Blood, and Lung Institute (NHLBI). She invited members to consider topics for the next meeting. The letter to the Secretary from SACHRP's last meeting, dated March 30, is now posted on the Web.

The minutes for February 2012 were approved without changes.

The Chair thanked Julia Gorey and Cecilia Chirinos, OHRP staff assigned to SACHRP, for their critical help in preparations for the meeting.

Report of Issues
Jerry Menikoff, M.D., J.D., Director, Office for Human Research Protections (OHRP)

Dr. Menikoff welcomed everyone. He said OHRP was busy working on a number of important cases that cannot yet be disclosed. The Education Division has been busy conducting meetings around the country dealing with international issues. The Division Director recently delivered a well-received and well-attended webinar on the "nuts and bolts" of regulations on the protection of human subjects.

On the policy front, the Food and Drug Administration (FDA) and OHRP are collaborating to finalize guidance regarding exculpatory language. Also, both agencies have recently released draft guidance regarding transfers of protocols from one IRB to another. Dr. Menikoff hopes that in the future it will be possible to issue joint guidance.

Regarding OHRP's recent Advance Notice of Proposed Rulemaking (ANPRM) seeking comments on possible regulatory changes to the Common Rule, comments are being reviewed internally. SACHRP's input is much appreciated.

The Director observed that local context, to be addressed by presentations at this meeting, has been a major issue since the regulations were first written. At that time, it was assumed that a local IRB would usually take responsibility for the entire protocol review process. In modern times, however, more

multi-center studies are common, and the issue of how best to address local context is more salient and complex. He said he would value SACHRP's input on local context.

Dr. Menikoff noted that two members of SACHRP have terms of service that are ending at this meeting. The first is David Forster, who has made "incredible contributions" and has a level of knowledge few can match. The time and effort he has given to SACHRP is extraordinary, and OHRP is grateful that he plans to continue his participation through his work on subcommittees.

Chair Barbara Bierer will also be leaving SACHRP, but the Director said he believed she would be present at the next meeting and planned to give a more complete discussion of her contributions at that time. He commented that SACHRP has been highly productive under her leadership and has taken on a number of important issues.

Dr. Bierer responded that the partnership among the committee, OHRP, and ex officios is essential to make good work possible. When there is a struggle to find the way forward, everyone gives their best thought and effort to the challenge, striving to address complex issues with integrity.

Subpart A Subcommittee (SAS)

David K. Nelson, M.S., CIP, SAS Co-Chair; David Borasky, M.P.H., CIP, SAS Co-Chair

Co-Chairs reviewed the charge of the subcommittee, its membership, meetings to date, and Secretarial letters that incorporate SAS recommendations. He noted that new members have reinvigorated the committee. Mr. Nelson also commented that David Borasky is moving to work with him at UNC-Chapel Hill.

Recommendations on Investigator Responsibilities

See:

- Attachment A. Investigator Responsibilities, As Presented
- Attachment B. Investigator Responsibilities, As Revised

Mr. Borasky explained that while the Common Rule sets out expectations for institutions and IRBs, it is virtually silent on the roles and responsibilities of the investigator, who interacts directly with subjects. Yet, even when the IRB has done its job well, institutions are held responsible for failures on the part of the investigator. In light of the recent ANPRM from OHRP and the possibility of rewriting the regulations, SAS has brought forward possible changes to address the investigator's role. SAS then presented draft recommendations regarding investigator responsibilities (see Attachment A).

Discussion

Defining "investigator." SACHRP members highlighted the importance of a more specific definition of investigator." SAS's initial definition read:

> *Investigators are the individuals that have direct contact with human research subjects and are in the best position to protect participants.*

A SACHRP member pointed out that even investigators who do not have direct conduct with subjects have significant responsibilities that should be addressed. For example, the person responsible for a

study site might not be the same person who designed the whole study. Dr. Joffe suggested specifying that an investigator could be responsible for the conduct of the study as a whole or at a specific site.

Dr. Allen suggested breaking out the roles of the Principal Investigator (PI), Co-Investigator, local site investigator, and sub-investigators and discussing each. While in a previous era the investigator was responsible for almost everything, today there is a complex infrastructure and responsibilities must be "teased out." He also observed that for a multi-site study, a committee might be involved in study oversight.

Dr. Rivera said it was confusing to try to define the roles of study staff; the important point was to identify someone who could be held responsible for enforcing any IRB provisions and ensuring compliance with the regulations. Mr. Forster cautioned against creating rules that leave no one clearly in charge.

A revised version presented by SAS later in the meeting read:

> *Investigators are the individuals who are responsible for direct contact with human research subjects, have direct oversight of study staff and trainees, and are directly responsible for the design, conduct and reporting of all human subjects research; investigators are in the best position to protect participants.*

Mr. Forster observed that a large study could have one PI in charge of 100 sites and an investigator on the ground at each site. Dr. Bierer stressed the importance of specifically including site investigators in the definition.

Mr. Forster pointed out that the study receptionist interacts with subjects but would not be considered an investigator. He said a clearer distinction was needed.

SACHRP advised that a definition of investigator should be included in the recommendations as well as in the introductory language. A revised version of the opening sentence of the recommendations read as follows:

> *§46.102 (Definitions)*
> *Investigator means any individual responsible for the conduct of human subjects research either for the study as a whole or at a particular site.*

Referencing Presidential Commission report. SACHRP decided to reference "Moral Science: Protecting Participants in Human Subjects Research," the recent report of the Presidential Commission for the Study of Bioethical Issues. The Commission specifically recommended that "the Common Rule should be revised to include a section directly addressing the responsibilities of investigators," arguing that this would "bring it into harmony with the Food and Drug Administration regulations for clinical research and international standards that make the obligations of individual researchers more explicit, and contribute to building a stronger culture of responsibility among investigators." A revised version of the recommendation letter presented later in the meeting quoted this statement and added, "We agree that encouraging a culture of responsibility among investigators is an important goal of human subject protection regulations."

Responsibilities of investigators (recommended regulatory language). In response to SACHRP members, several changes were made in this section:

- In section (a), placing "the IRB study plan" before "the terms of the grant…" since the IRB also has to review the grant.
- In section (d), specifying "as approved by the IRB." Members noted that the IRB is free to impose standards more rigorous than those stated in §46.116 and §46.117.
- In section (e), deleting the word "protocol" to avoid implying that the waiver is part of the protocol.
- A new responsibility was added: " Investigators are responsible for ensuring that study staff and trainees are appropriately qualified and trained."

SACHRP discussed section (g) extensively. The draft version read:

> *Investigators are required to permit and facilitate monitoring and auditing, at reasonable times, by the IRB of record, funding agencies, sponsors, the Secretary, and other federal and state regulatory agencies, as appropriate.*

Discussion points raised by SACHRP members included:

- If a company is providing the study drug, it should be considered a sponsor.
- The responsibilities of sponsors are not limited to funding; they belong in the list.
- An important responsibility of the investigator is ensuring that study staff are qualified and appropriately trained, Dr. Allen pointed out. However, another SACHRP member said that there were instances in which staff are hired by the Department and the investigator has no input into their selection. In such cases, another suggested, the investigator should fire anyone who is not qualified and trained.
- Dr. Bierer noted that current OHRP guidance says that investigators include anyone involved in conducting the research, a position incompatible with that of the FDA.
- A SACHRP member commented that design, which has been identified as an investigator function, is sometimes done by other people. However, it would be unethical for an investigator to agree to conduct research that is not appropriately designed.
- A SACHRP member questioned whether design and reporting belonged in the scope of investigator responsibilities. Dr. Joffe pointed out it was hard to hold a person responsible for design work that occurred prior to IRB review.

A revised version of this section changed "funding agencies" to "funding entities" but left it otherwise the same.

Qualification standards for investigators (recommended regulatory language). SACHRP members proposed several changes to the initial draft:

- Dr. Joffe preferred the word "must" to "should" in relation to assuring sufficient time and resources were available, noting that it was a "stronger word."
- Dr. Rivera questioned the enforceability of issues related to time and resources, as well as the extent to which investigators could control these variables completely. She asked whether overspending was now to become an IRB issue. Dr. Joffe said it was the investigator's

responsibility to at least go to the institution or sponsor and request the resources needed. Dr. Ross said this should be seen as the responsibility of the lead investigator only.

- Dr. Joffe said the standards should be consistent with wording in the section on investigator responsibilities, for example, in addressing design and reporting.
- In regard to "sufficiently qualified" investigators, Mr. Nelson mentioned a study in which third graders were involved in community research but were determined to be appropriately qualified to be investigators for the purposes of that study.

Investigator records, reports, and documentation (recommended regulatory language). SACHRP revised the reference to safe and secure storage of research data " in both paper and electronic formats" to clarify that the intent was to ensure this was done for data in either format:

> *Investigators are responsible for the safe and secure storage of research data (**whether in paper or electronic formats**) and for adequately protecting the confidentiality of the data.*

Dr. Rivera questioned the original wording of (b), which read:

> *Investigators are responsible for the accuracy and completeness of the data recorded and reported in research and in publications about the research.*

She said it implied that OHRP and the IRB would be involved in issues surrounding research integrity. Also, confidentiality is not always required. Mr. Nelson observed that while ensuring accurate reporting is part of the investigators' responsibility in a global sense, it may not be part of the regulations. Dr. Menikoff clarified that OHRP does not typically go after investigators directly, but assumes that compliance actions will ensure that institutions take their oversight responsibilities seriously. The sentence was revised to:

> *Investigators are responsible for the accuracy and completeness of **study data.***

Dr. Bierer commented that it may be a "major stretch" to address the design as well as the conduct of research in the regulations.

Dr. Allen suggested replacing "when the research ends" with the following more precise wording: "at the completion of the study."

Action

SACHRP asked SAS to continue working on the document and bring a revised version to the committee's October meeting.

Consent and Waivers

See:

- Attachment C. Consent and Waivers, As Presented
- Attachment D. Consent and Waivers, As Revised

Dr. Menikoff invited SAS to address issues related to consent and waivers, in part because of concerns that the regulations may be implemented differently at different institutions and justice issues have

arisen. Co-Chairs noted that although SAS has already developed recommendations on consent and waivers, the recent ANPRM has opened the opportunity for substantive changes in the regulations that were not considered when these recommendations were developed. For example, the precise meaning of the term "practicability," which is one of the criteria for waivers, is not clear. Given this opening, SAS drafted recommendations that would require regulatory changes (see Attachment C).

Discussion

Introduction. Dr. Bierer suggested adding an example to illustrate the addition of valueless documents to the consent process. SAS added the example of a statement that "the only alternative is not to participate in this research."

SACHRP members also differed with the statement that IRBs have "consistently" required investigators to include information in the consent process that are without value. The statement was revised to say this "frequently" occurs.

Additional changes were made for grammatical reasons (maintaining parallel structure in paragraph four) and to improve the readability of the metaphor in the penultimate paragraph of the introduction (from "would not erode the bedrock ethical component that is informed consent" to "would not erode the ethical foundation embodied in informed consent").

Elements of consent. Dr. Bierer commented that OHRP has expressed interest in whether any of the existing elements of consent should be challenged as regulations are rewritten. SAS felt there was merit in looking at both the "basic" and "optional" elements of consent but focused primarily on the issues surrounding waivers. In the draft presented, all elements were identified as "basic."

Mr. Nelson clarified that it was not SAS's intent that any of the fourteen elements be required in all cases. Dr. Rivera was uncomfortable with any wording that would imply all of them are optional, forcing IRBs to make an affirmative decision that any elements should be addressed.

SACHRP revised the draft to separate out "basic" and "optional" elements of consent.

Dr. Chadwick pointed out that section 116 (c) of existing regulations, which relates to waivers of informed consent for local and state government research, was missing and should be reinserted.

Dr. Rivera said she would like to see SACHRP address the issue of compensation for injuries incurred in the course of research, a subject raised by COL Nelson Michael of the Presidential Commission for the Study of Bioethical Issues in a February, 2012 presentation to SACHRP. She found the current language in SAS's draft recommendation, which requires only that the subject know "whom to contact in the event of a research-related injury," to be "wishy-washy." Mr. Forster said he would like to see SACHRP go on record as supporting compensation. He pointed out that the Commission had suggested that SACHRP take up this issue. Dr. Menikoff commented that it is "not for one committee to tell another what to do." Asked why SACHRP could not examine the issue if several members wanted to do so, Dr. Menikoff stressed that SACHRP's role is to "advance the agenda of HHS."

Dr. Bierer suggested that the element that mentions compensation be identified as "optional."

Members differed on the issue of whether the presentation of alternatives to study participation should be identified as an optional or required element. Dr. Joffe was concerned that it would not get the attention it deserves if identified as optional. He suggested identifying it as required but noting that a statement to the effect that the only alternative is not to participate in the research is not necessary.

Research involving records or specimens not collected for research purposes. SAS's original proposal reads as follows:

> *(b) Unless the IRB determines otherwise, informed consent is not required for research involving records or specimens that have been collected for non-research purposes, provided that:*
>
> *(1) There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data; and*
>
> *(2) There will be no attempt on the part of investigators to contact subjects for research purposes.*

Dr. Joffe suggested revising "records or specimens that have been collected for non-research purposes" to "records or specimens that have been *or will be* collected…". Dr. Allen agreed that the statement should include both, addressing a "big loophole." Dr. Bierer said the difference between research and non-research needed to be parsed.

Dr. Bierer observed that recontacting subjects may be a violation of privacy.

Dr. Ross asked why, when it is known that samples will be in demand for research, subjects should not be told that discarded materials will be used for this purpose. Dr. Menikoff added that required consent is the "default" position of new regulations as envisioned in the ANPRM.

Mr. Forster felt the language as written would "open the door too wide" and suggested it be dropped. Others agreed.

Conditions for a waiver. Committee members debated conditions for waivers, especially "scientific" or "ethical" justifications. Dr. Joffe observed that the rationale for waivers of consent to research would always be logistical or scientific rather than ethical. Mr. Nelson countered that ethical concerns exist that do not depend on science, such as the possibility of psychological harm.

Revisions. On the second day of the SACHRP meeting, SAS presented a revised version of the draft that incorporated changes suggested by SACHRP. The new draft reinstated regulatory language related to waivers. The word "reasonable" replaced the problematic word "practicable" in the existing regulations. The list of required elements was reduced to five. Nine elements were identified as optional. The reference to compensation was eliminated, but SAS still included a reference to the need to name a contact in the event of injury.

In regard to conditions for a waiver, Dr. Chadwick questioned the inclusion of "ethical or scientific justification" and "a scientifically and ethically justifiable rationale why the research could not be conducted with another population from whom consent could be obtained." He suggested these items belonged in guidance rather than in the regulations and should be dropped. Others agreed. However, Dr. Allen felt that omitting the following would be "a loss": "The waiver of consent is not justified solely on the basis of convenience, cost, or speed."

Dr. Bierer questioned the word "whenever" in the following condition for a waiver: "*Whenever* appropriate, the subjects will be provided with additional pertinent information after participation." Observing that this typically applies only to research involving deception, she suggested the word "if" was more appropriate. The change was made.

Dr. Allen was uncomfortable with deleting the reference to an "ethical or scientific justification." Dr. Bierer observed that an IRB cannot approve research that is not scientifically justifiable. Mr. Forster said the condition would be too stringent for some research, such as student-conducted studies. The chair took a vote on reintroducing the reference to scientific justification. The majority wanted to omit it.

Dr. Menikoff commented that one concern in the current system is the variability in how IRBs interpret the current language. He was uncertain what SAS's recommendations had to say about whether or not "generic" chart reviews could be waived.

Action

The Committee asked SAS to give further attention to the document and bring a new version to the October meeting. Dr. Joffe and Dr. Bierer volunteered to work with SAS on the new draft.

Internet Research

Elizabeth Buchanan, Ph.D., Director of the Center for Applied Ethics, University of Wisconsin-Stout; Dean R. Gallant, A.B., Assistant Dean for Research Policy and Administration, Harvard University

Note: PowerPoints for all presentations are posted on the OHRP Web site. Please see these resources for more detailed information.

Dr. Buchanan led a previous SACHRP panel on the same topic July 20-21, 2010, in which four panel members spoke about different aspects of Internet research. The goal of that panel was to open the conversation about the interface between the internet and research. The speaker noted that the Common Rule predates the internet and does not address specific issues. To fill the gap, institutions are developing their own policies and procedures, some of which are inconsistent.

Research-related uses of the internet encompass collecting or analyzing information available on the Internet without directly interacting with research subjects (for example, "scraping" data from social media profiles); using the internet as a tool for recruiting or interacting with subjects; conducting research about the Internet itself, such as analyses of network traffic; Internet-based clinical trials; and online experiments.

Speakers felt that a "Points to Consider" document on Internet research would fill a need and help to focus further discussion. They focused their presentation on elements they believed should be addressed in the document and requested SACHRP members' response.

Dr. Buchanan distinguished between "engaged" and "non-intrusive" types of research, noting that these exist on a continuum rather than as either/or choices. Distinctions focus on how close the researcher is to the subject. Dr. Buchanan said these distinctions pointed to methodological issues in

protocol review. However, Dr. Bierer questioned whether everything could be placed in these "large buckets." Dr. Buchanan stressed that they should be considered as representing a continuum of issues rather than a "binary" approach.

SACHRP members suggested that it would be helpful to clarify in what instances internet research can be compared to the familiar "public park" scenario, in which people clearly know they are in a public space where their behavior might be observed.

Ms. Krivacic asked what it would take to consider research as "intrusive." Dr. Buchanan said there is an abundance of literature about chat rooms, where research requires careful planning. Sometimes the researcher is told he or she is not welcome on the site. Some sites have proactively developed rules stating how research will be handled. If the researcher uses the real names of chat room visitors, explicit consent should definitely be required. Dr. Ross pointed out that researchers might not always know that a subject considers information to be "sensitive."

Examples of Guidelines for Internet Research

http://irb.uconn.edu/Internet_research.html

http://www.marianuniversity.edu/interior.aspx?id=13714

http://inside.bard.edu/irb/guidelines/

http://www.luc.edu/irb/irbonlinesurveys2.shtml

http://www.research.psu.edu/policies/research-protections/irb/irb-guideline-10

Major issues highlighted by speakers include data identifiability and subject privacy, informed consent, data security, data sharing, the application of "local context" to the internet, and prevailing standards of conduct. They identified the following key questions to explore as guidance is developed:

- *What is nonexempt research involving HS on the internet?* Examples of issues include whether avatars and other Internet personae should be considered "persons."

- *What is "identifiable private information" on the internet?* Dr. Bierer noted there could be significant consequence to tracing subjects to their IP address. She observed that the issue is not unique to the Internet. Ms. Krivacic said tracing the IP address could place people who believed their responses were anonymous at risk. A speaker suggested that any website for which membership must be authorized by a separate entity should be considered private for the purpose of determining eligibility for exemption. Dr. Bierer pointed out that websites can change their policy, and data that were considered private could become public.

- *What can subjects "reasonably expect" regarding privacy?* Dr. Allen suggested that the ease with which information could be accessed is a consideration. A member commented that in an age in which apps make it possible for people to broadcast their exact locations, people should be "looking out for themselves."

- *What is intervention or interaction with a research subject on the internet?* Speakers noted that a researcher could set up a mirror room for research purposes (for example, an island in "Second Life"). Also noted was the use of "mechanical turks" to recruit subjects for focus groups. Focus groups, direct dialogue, social media exchanges, online surveys, text messages, and "chats" could all be considered as interactions with subjects.

- *What are characteristics of purely public sites?* Speakers stressed that the researcher is responsible for knowing the community norms that apply to a given site. IRBs will need to consider how researchers came to possess their data. Mr. Gallant said the individual's expectations at the time that he or she created the data are critical. Dr. Allen noted that, increasingly, information is made public inadvertently; researchers should take care not to compound such injuries.

- *When is information recorded in an identifiable manner?* Most, if not all, data on the Internet have been "recorded" in some fashion, often with identifiers attached.

- *When are data, documents, or records considered "publicly available" when posted on the Internet?* Speakers suggested that a "tiered standard" is required to address this issue. Mr. Gallant pointed to the requirement that a fee be paid to access data as one dividing line. However, Dr. Joffe did not feel that the need to pay for access to the data was relevant to the issue of whether data should be considered public or private.

- *How do investigators obtain informed consent/parental permission/assent of subjects for research on the Internet?* States have different ages of majority, and subjects frequently misrepresent their ages.

- *What forms of online advertising and recruitment are used and what is reviewable by an IRB?* OHRP considers subject recruitment to be part of the informed consent process.

- *When may investigators seek to waive or alter the informed consent of subjects in research on the internet?* Completion of online surveys or tests might be considered as indications of "passive" or "applied" consent. However, the possibility of children being involved without the researcher's knowledge or intent must be considered. Mr. Gallant said if the researcher does not know who the subjects are, the assumption should be that some of them are minors. Without some method of age confirmation, the IRB might say such research can only be approved under Subpart D.

- *How do investigators document the informed consent of subjects for research on the internet?* Challenges may arise with minors. For example, attendees at a recent meeting of Public Responsibility in Medicine and Research (PRIM&R) discussed a study involving gay teens in the south, which remained in review for 17 months. Also in regard to this question, both OHRP and FDA have FAQs that indicate that electronic signatures may be acceptable.

- *What is the "local research context" in internet research?* Dr. Menikoff commented that the context should be considered to be the subject's community, which could be a fantasy world on the Internet. Dr. Pritchard observed that community consultation is an important aspect of this issue.

- *What is "minimal risk" in internet research?* Speakers saw many "haunting questions" in this area, including to what extent daily life in the age of the Internet is different from daily life in other periods.

- *How can investigators minimize the risk of harm when using sensitive online data?* A variety of issues arise, including the need to disclose whether data are potentially identifiable and how long data may be stored "in the cloud."

Discussion

SACHRP discussed many issues as they arose in the presentation. Their comments are included above.

In regard to how internet issues might be addressed in revised regulations, Dr. Menikoff said he was not aware of unique issues. Dr. Buchanan agreed, suggesting that issues surrounding identifiable data were "just bigger" and "more extreme."

Dr. Rivera asked about the relevance of a provision included in the recent ANPRM from OHRP regarding the use of a minimum standard for data security. Dr. Bierer observed that members of the Association for Internet Researchers, the majority of whom are communication scholars, objected strongly to this provision as "way too high" for most internet research. Dr. Buchanan said that having someone on the IRB who is familiar with internet research is a necessity.

SACHRP members provided feedback to speakers regarding the proposed "Points to Consider" document. Members suggested using examples, but with language that will stand the test of time. They also suggested considering risks for different age groups and offering examples of how the elements of consent can be addressed in the context of internet research. The University of Washington was said to have useful models for handling consent on the Internet. Dr. Bierer asked SACHRP members with additional suggestions to communicate them to the speakers.

Public Comment

Public comment was invited, but no comments were offered.

Wednesday, July 11, 2012

Considering Local Context

Ivor Pritchard, Ph.D., Senior Advisor to the Director, OHRP

Dr. Pritchard said OHRP would welcome guidance from SACHRP on how issues surrounding local context might be addressed in new guidance. He pointed to a "Goldilocks problem" associated with local context: IRBs need enough information to approve a study but not so much that the IRB is collecting useless information that will not help it does not help the IRB ensure the right protections. Local context may encompass state and local laws and regulations, subject populations, investigators' qualifications, and issues regarding the institution where the research will be conducted (e.g., the quality of its facilities).

There is little guidance in the regulatory text about local context. It is a term of art that arises in reference to IRB membership, which must include people who are sensitive to "community attitudes," and that some consider relevant to the protection of vulnerable populations. As multi-site studies become increasingly common, local context has been spotlighted as an issue that must be addressed. OHRP (then OPRR) wrote a memorandum on IRB Knowledge of Local Research Context (July 21,

2000) that states that OHRP must approve arrangements for cooperative review. This is not OHRP's current position, and the memo may have resulted in excessive attention to local context.

Dr. Pritchard highlighted various mechanisms for assessing local context. They include central or local IRB members, investigators, consultants (an option that is not used often because of practicability, logistics, and the need for planning), staff research, and community representatives.

OHRP's recent Advance Notice of Proposed Rulemaking (ANPRM), "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators," included relevant questions:

> How does local IRB review of research add to the protection of human subjects in multi-site research studies? How would mandating one IRB of record impair consideration of valuable local knowledge that enhances protection of human subjects? Should the public be concerned that a centralized IRB may not have adequate knowledge of an institution's specific perspective or the needs of their population, or that a centralized IRB may not share an institution's view or interpretations on certain ethical issues?

Public response was generally in favor of using a single IRB for multi-site studies. Some concern was expressed about whether communities would be able to communicate their concerns. A respondent pointed out that some institutions might object to a study that is not objectionable to others (for example, a Catholic institution might object to a study that requires a female to take contraceptives). Institutional procedures and investigator qualifications are also relevant.

Dr. Pritchard noted that OHRP has had few compliance cases in which local context was a factor, and those that do exist are not recent. Few questions come to OHRP from the public about local context. He said that OHRP has no way of knowing how frequently local context becomes a difficult issue for IRBs.

The speaker raised the following questions:

- How should knowledge of the local research context be delivered through the standard application process?
- How should knowledge of the local research context be delivered through other means from other sources (e.g. IRB staff, consultants)?
- When is verification of submitted information from various sources regarding local context required or recommended?
- What about other local knowledge?

The speaker said that IRBs that handle a large volume of protocols probably do a good job of capturing "known unknowns" when working with protocols for other sites. Ideally, Dr. Pritchard said, what is needed is an approach that captures relevant "unknown unknowns" but does not waste time on the irrelevant ones. It would be helpful to have diagnostic questions that focus on what is most likely to be relevant.

Discussion

Dr. Bierer observed that OHRP has not yet stated what elements of local context are most salient in particular studies. Dr. Pritchard responded that these are generally the types of things identified in public responses to the ANPRM question cited above, though OHRP did not receive clear direction from respondents on how the labor of addressing local context should be divided in multi-site studies. He noted that some of these issues are addressed in inclusion/exclusion criteria, such as the need for consent forms to be translated.

Dr. Rivera suggested that a sample "smart form" with branching options might be helpful to investigators and IRBs. She felt that having hundreds of institutions developing their own forms and approaches would be wasteful. Another SACHRP member suggested that it might be possible to learn from the experience of countries that have a national or regional system for reviewing studies, such as Germany and Belgium. Many of them have both central review mechanisms and local groups. In response to a question from Dr. Menikoff, a SACHRP member estimated that significant issues regarding local context typically arise in only about 5 percent of the protocols reviewed.

A panel member noted that FDA, like OHRP, has issued guidance on local context, and asked whether the two agencies' guidance could be the same. Dr. Menikoff said that OHRP works closely with FDA on this and other issues. Dr. Pritchard observed, however, that the research FDA oversees is different in some significant ways from the research OHRP oversees, and guidance may need to take those differences into account.

Dr. Joffe commented in reference to multisite research, the issues surrounding ethical review and day-to-day implementation are conceptually different. The latter is largely a function of staff at the local level. Dr. Pritchard observed that it is challenging to assemble a diverse IRB that is prepared to handle ethical issues for a wide range of studies.

Subcommittee on Harmonization (SOH)

David Mr. Forster, J.D., and Mark Barnes, J.D., SOH Co-Chairs

Mr. Forster reviewed the charge of the subcommittee, its membership, meetings to date, and Secretarial letters that incorporate SOH recommendations. He then reviewed draft comments from SOH on the issue of local context. He noted that today's comments do not focus on constructive solutions, but rather on describing the problems.

Mr. Forster stressed that the guidance on local context posted on the OHRP website is still the "go to" document for the field, even though it does not reflect OHRP's current position. Members suggested that OHRP archive the document to avoid confusion, but Dr. Menikoff said there were legal issues that had to be dealt with when guidance was archived. Dr. Chadwick observed that the local context guidance from the Office for Protection from Research Risks (now OHRP) regarding the use of an independent IRB has added to the confusion at his university around how local context should be addressed.

After reviewing current existing guidance on local context, SOH recommended that both FDA and OHRP revise their guidance documents or issue new harmonized guidance. SOH also proposed that the term "local context" be retired as unhelpful.

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SOH/SACHRP recommends that OHRP and FDA retire their respective guidance documents and issue guidance, which encourages single IRB review under a "reliance model" that allows an institution to use an external IRB (whether central or independent or other type of single IRB review model) that is deemed competent if its policies and procedures comply with the federal regulations related to IRB composition and review procedures. The use of the term "local context" should be expunged.

See:

- Attachment E. SOH Draft Comments on Local Context

Mr. Forster observed that local context becomes a key issue in international research, which always requires teleconferences or other mechanisms to get "real time" direct input on often profound cultural issues. In addition to questions researchers would commonly ask, issues often arise that researchers would not expect in advance. These could be considered "unknown unknowns."

Difficulties arise in using consultants to provide such input, in that they may not be familiar enough with the details of the research to provide on-target advice. Often, when a central IRB requests such input from local sites, they ask, "isn't this your job?" It is not clear whether the local coordinator for the research is a suitable person to fulfill this role from OHRP's perspective.

Dr. Allen commented that the Presidential Commission for the Study of Bioethical Issues, in its recent report, "Moral Science: Protecting Participants in Human Subjects Research," seemed to imply that investigators should explore such questions as part of the study design process.

Discussion

Dr. Rivera observed that many IRBs turn to the OHRP website for guidance and would have no way of knowing that OHRP's existing guidance regarding local context no longer reflects its position. She suggested the guidance be annotated or archived. Dr. Menikoff said that archiving documents raises legal challenges and that OHRP has communicated its new position through several channels, including SACHRP minutes. Dr. Allen stressed that the guidance should not simply be removed unless it is replaced with new guidance, since it is important that issues surrounding local context be considered.

In response to a question regarding its approach to local context, Dr. Cates, an ex officio representative of the Department of Veterans Affairs (VA), said the VA "takes it seriously." Local facilities are instructed to research state and local laws pertaining to the research, such as those related to research-related injuries; finding and updating them is a "huge job." The VA relies on regional counsel for assistance. In addition, cultural differences among veterans, including Spanish-speaking veterans, must be addressed.

Members saw the need for a data base of laws and regulations pertinent to human subjects protection, noting it made no sense for IRBs nationwide to be doing the same search for this information. Dr. Bierer saw this as a possible contribution OHRP could make to the field. A member observed, however, that keeping the data base updated would be challenging and labor intensive.

The Chair also suggested that many of the questions to be explored could be captured in an online form similar to tax preparation software. These could capture the features of local context that really drive decisions. She noted that subtle questions that require real cultural sensitivity arise infrequently.

Action

Members declined to approve the recommendation from SOH on local context on the grounds that, as one said, "we already know all this" and it does not contain the practical suggestions OHRP was hoping to receive from SACHRP.

Instead, members encouraged SOH to proceed with next steps and develop practical, "positive" recommendations to address the issues that arise in the field. The introduction to the document should make clear that SOH is addressing the issue of local context at the request of OHRP.

A Reconsideration of Group Harm

Dr. Lainie Ross, M.D., Ph.D., Department of Pediatrics, University of Chicago; Daniel Hausman, Ph.D., Department of Philosophy, University of Wisconsin-Madison

Remarks by Lainie Ross

Dr. Ross observed that groups and communities are not "human subjects" under the federal regulations governing research, yet both the members of the groups who participate (and possibly the non-members) are at risk of outcome harms. Most people belong to many groups, and membership may be defined at birth or later in life. Traits that define membership may be permanent, such as those due to genetic inheritance, or may be transient due to changing preferences or geographic mobility.

The speaker defined research-related risks as level A, B, or C, as shown in the following table:

LEVEL OF RISK	Process-Related Risks to Well-Being	Outcomes-Related Risks to Well-Being	Risks to Agency
A Individual (Research subject)	Clinical and psychosocial risks of the research interaction	Clinical and psychosocial risks of research findings	Risk of undermining personal autonomy/ authority
B Individual by group association (may or may not be research subject)	Clinical and psychosocial identity risks of the research interaction	Clinical and psychosocial identity risks of research findings	Risk of group decisions undermining personal autonomy/authority (bi-directionality)
C Community (whose members are research subjects, in part b/c on their membership)	Risks to group cohesion or structure because of engagement in research	Risks to group cohesion or structure because of research findings	Risk of undermining the group's moral and sociopolitical authority

She argued that different entities were best equipped to assess the various types of risk:

- The individual investigator must be concerned about all risks (A, B, and C).
- The IRB should focus on A-level risks and may also ask researchers to consider risks related to outcomes at all three levels.
- The conflict of interest committee will need to focus on risks related to outcomes at all levels and "ensure that agency is robust."
- The Research Ethics Consultation (REC) program may be concerned about any and all risks.
- The Research Subject Advocacy (RSA) program may want to focus on A-level risks, but may also consider agency risks at all levels.

The federal regulations do not require IRBs to evaluate the risks to groups, but the risks are real and they should be considered. Dr. Ross proposed that:

- IRBs should ask researchers to consider the group and community risks that their research poses and to discuss how these will be managed.
- Group risks should be identified and discussed in the consent form

Remarks by Daniel Hausman

Dr. Hausman stressed that group harms can be serious and must be addressed. Like Dr. Ross, he classified harms according to those related to process and those related to outcomes as shown on the table. He argued that different criteria should govern the protection of research subjects than should govern the protection of third parties. While informed consent is required for individual subjects, he said that in many cases, it is not feasible to have informed consent with respect to third-party or structured groups.

Harms	Process-related	Outcome-related
Harms to structured groups	Disrupting	Undermining
Group-mediated individual harms	Stigmatizing	Stereotyping
Other third-party harms	Contagion	Exploitation

The speaker felt strongly that IRBs are not well suited to address problems related to possible group or other third-party harms. He argued that asking them to do so would be an "enormous amplification of their responsibility."

Actions that should be taken to protect groups from harm include:

- Inform individual research subjects of group risks.
- Inform structured groups of research risks and benefits.
- Aim for collaboration with legitimate leadership of structured groups.
- Seek knowledge of what might be stigmatizing or stereotyping and how to limit these risks. Seek to understand.

Discussion

Many members took issue with Dr. Hausman's contention that group harms should not be addressed by the IRB, noting that it is the IRB's task to weigh the benefits and harms related to the research

process. Dr. Allen saw IRBs as focusing on process-related harms. He argued that research has consequences for third parties as well as for structured groups that should be considered. Another SACHRP member agreed that some direct, process-related third-party harms might need to be considered by IRBs.

SACHRP also discussed the challenge of identifying appropriate representatives for groups to provide their perspective on potential group harm. In some cases, the community is involved in research development and implementation, and the research team might actually be part of the group. In others, the process for identifying appropriate spokespersons requires an extra step. The Chair noted that there is no mandate for IRBs to ensure group involvement. She wondered who should be considered responsible for ensuring appropriate group participation. Another member noted that designated leaders may still be out of touch with some constituents (for example, a tribal leader who cannot speak for those who live off the reservation). Attending to the concerns of groups, Dr. Allen said, can lead to serious questions of equity.

Members discussed whether the regulatory framework should be changed and whether best practices should be identified to ensure respect for groups. The Chair suggested approaching the subject "gingerly," especially in regard to unstructured groups. She saw the need for a process in which potential harms to structured groups receive due consideration so that groups are protected from unintended consequences. She also pointed to the difficulty of defining communities and providing helpful counsel. Dr. Ross observed that members of the Havasupai tribe were harmed as a result of their participation in research, yet no regulations were violated by researchers. It is a challenge to see what should have been done, in retrospect, to prevent harm.

SACHRP members sought examples of possible third-party harms in order to clarify how they should be addressed. Mr. Forster introduced the example of vaccine studies. He asked whether subjects have the right to withdraw, given the potential to infect the community. Dr. Ross suggested that there may be cases in which information might cause harm to third parties. Ms. Krivacic gave the example of a Central Intelligence Agency study of ethnic groups in a war-torn area in which leaked information could lead to the murder of a community or family member. Mr. Forster noted that there are also possible group-level benefits from participation in research; for example, some international researchers identify country-level benefits such as leaving a lab behind for national use.

Dr. Joffe suggested two ways of framing related issues. One issue is whether changes in the regulatory framework are needed to adequately address group harms. Another is the possible need to identify best practices to ensure appropriate respect to groups. Dr. Ross noted that developing best practices may be complex as a result of the many different kinds of groups (e.g., neighborhoods vs. social networks) and the many variables (for example, groups to which people do not know they belong). While guidance might suggest the need for a letter from leaders of structured groups regarding the group's participation in research, it is not clear what could be done to address possible harms to unstructured groups.

Dr. Rivera suggested removing prohibitions that would keep IRBs from thinking beyond the level of individual participation so they are free to consider possible harms. However, Dr. Bierer said that nothing in the regulations prohibits considering benefits and harms beyond the individual. She saw a need to specifically define groups as subjects, to describe a process to consider risks to structured groups, and to reach clarity about who is responsible for ensuring any risks are considered and addressed.

Dr. Rivera suggested revising the regulations to make it clear that IRBs can consider third-party harms. She pointed to the following statement in the regulations:

> The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility (45 CFR 46.111).

She suggested that this statement be revised to clarify that third-party harms could be considered.

SACHRP agreed to ask SAS to consider the issues discussed and come to the October meeting with specific recommendations.

Agenda for October 2012

The next meeting will review issues surrounding electronic signatures. It will also consider revised recommendations from SAS regarding the Principal Investigator's roles and responsibilities, as well as consent and waivers. SAS may also have a recommendation on group harm. In addition, the meeting is expected to include a review of a Points to Consider document on issues related to the internet and recommendations from SOH on local context.

Other subjects that might be addressed include deception research (Mr. Forster said SOH had a draft in progress), the issue of what constitutes "undue influence," and "adaptive vs. clustered vs. randomized" clinical trials.

Public comment was invited, but no comments were offered.

Attachment A. Investigator Responsibilities, As Presented

Draft Investigator Responsibilities Requirement for SAS consideration

Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Sebelius:

In accordance with the provisions of the charter for the Secretary's Advisory Committee on Human Research Protections (SACHRP), I respectfully submit for your consideration a recommendation relative to Department of Health and Human Services Regulation for the Protection of Human Subjects as codified in 45 CFR Part 46. This letter represents the xxx in a series of recommendations from SACHRP.

The HHS 45 CFR 46 Regulation for the Protection of Human Subjects in Research, unlike FDA regulations, does not directly address the roles and responsibilities of investigators involved in human subjects research. Investigators are the individuals that have direct contact with human research subjects and are in the best position to protect participants. While IRBs serve a critical function, they are removed from the day-to-day research activities and thus their ability to monitor research activities is limited. The NIH and FDA have partially addressed the need for enhanced focus on investigator responsibilities through training in grant requirements, guidance and product approval regulations; however, these regulations address only clinical and biomedical investigators.

SACHRP proposes the addition to 45 CFR 46 of three sections that would cover, at a minimum: (1) responsibilities of investigators; (2) qualification standards for investigators (e.g., training); and (3) investigator documentation/records.

New regulations to ensure investigator accountability would codify the current ethical expectations for investigators who conduct human subjects research. Regulations addressing investigator responsibility should emphasize the critical role of the investigator and hold the investigator directly accountable for his/her actions. As part of the FWA requirements, institutions are responsible for ensuring that the regulations are effectively applied. The oversight authority (45 CFR Part 46.103(a)) is already in place: "each institution engaged in research … shall provide written assurance … that it will comply with the requirements set forth in this policy."

Adding investigator responsibilities to the HHS regulations would harmonize HHS regulations with those of the FDA and international standards, uniting the regulatory expectations. Models for delineating investigator responsibilities can be found in the drug and device regulations of the FDA (i.e., Subpart D, 21 CFR Part 312 and Subpart E, 21 CFR Part 812) and in internationally accepted guidelines such as the ICH standards (Good Clinical Practice E-6, Section 4) and the CIOMS International Ethical Guidelines For Biomedical Research.

Therefore, SACHRP recommends the following language for inclusion in 45 CFR 46:

§46.104 Responsibilities of Investigators.
(a) Investigators are responsible for ensuring that research is conducted according to:
(1) sound research design and scientific methods;

(2) the terms of the grant, contract and/or signed funding agreements, that are applicable to the investigator;
(3) the IRB approved study plan (protocol);
(4) applicable laws and regulations including those for protecting the rights, safety, and welfare of human subjects.

(b) Unless exempt from review, investigators are responsible for obtaining initial IRB approval, prior approval for any modifications to the research and, as required, continuing review of the research.

(c) Investigators are responsible for providing the IRB with sufficient information and materials to make the required determinations in §46.111.

(d) Unless waived by the IRB, investigators are responsible for ensuring that informed consent is obtained in accordance with §46.116. Unless waived by the IRB, investigators are responsible for obtaining signed consent to the extent required by §46.117.

(e) Investigators are responsible for providing a copy of the informed consent to each subject, unless the requirement of a written consent document is not part of the IRB approved protocol.

(f) When vulnerable populations are involved in research, investigators are responsible for complying with any required additional safeguards.

(g) Investigators are required to permit and facilitate monitoring and auditing, at reasonable times, by the IRB of record, funding agencies, sponsors, the Secretary, and other federal and state regulatory agencies, as appropriate.

(h) In compliance with §46.103(b)(5) of this subpart, investigators shall ensure prompt reporting to the IRB of any noncompliance with the approved protocol or requirements of the IRB, and unanticipated problems involving risks to subjects or others.

(i) Investigators are responsible for personally conducting or supervising the research.

(j) Investigators are responsible for complying with regulatory and institutional requirements including those relating to financial interests that are relevant to the research

§46.105 Qualification Standards for Investigators.

(a) Investigators must be sufficiently qualified by education, training, and experience that is appropriate to their role in the research to assume responsibility for the proper conduct of human subjects research.

(b) Investigators should have sufficient time and resources to properly conduct or supervise the research for which they are responsible.

§46.106 Investigator Records, Reports and Documentation.

(a) Investigators are responsible for the safe and secure storage of research data (in both paper and electronic formats) and protecting the confidentiality of the data.

(b) Investigators are responsible for the accuracy and completeness of the data recorded and reported in research and in publications about the research.

(c) Investigators must maintain records appropriate to the research (e.g., the study plan, consent forms, and correspondence from the IRB) and permit inspection of the research records in accordance with §46.104(f).

(d) Investigators must maintain records for at least three years after the research ends or for the length of time specified in applicable regulations or applicable institutional or sponsor requirements, whichever is longer, and should take measures to prevent accidental or premature destruction of these documents.

(e) Investigators must submit written reports to the IRB as requested/required by the IRB.

Attachment B. Investigator Responsibilities, As Revised

Draft Investigator Responsibilities Requirement for SAS consideration

Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Sebelius:

In accordance with the provisions of the charter for the Secretary's Advisory Committee on Human Research Protections (SACHRP), I respectfully submit for your consideration a recommendation relative to Department of Health and Human Services Regulation for the Protection of Human Subjects as codified in 45 CFR Part 46. This letter represents the xxx in a series of recommendations from SACHRP.

The HHS 45 CFR 46 Regulation for the Protection of Human Subjects in Research, unlike FDA regulations, does not directly address the roles and responsibilities of investigators involved in human subjects research. Investigators are the individuals **who are responsible for** direct contact with human research subjects, **have direct oversight of study staff and trainees, and are directly responsible for the design, conduct and reporting of all human subjects research; investigators** are in the best position to protect participants. While IRBs serve a critical function, they are removed from the day-to-day research activities and thus their ability to monitor research activities is limited. ~~The NIH and FDA have partially addressed the need for enhanced focus on investigator responsibilities through training in grant requirements, guidance and product approval regulations; however, these regulations address only clinical and biomedical investigators~~.

In the recent report "MORAL SCIENCE: Protecting Participants in Human Subjects Research," the Presidential Commission for the Study of Bioethical Issues recommended that "The Common Rule should be revised to include a section directly addressing the responsibilities of investigators. Doing so would bring it into harmony with the Food and Drug Administration regulations for clinical research and international standards that make the obligations of individual researchers more explicit, and contribute to building a stronger culture of responsibility among investigators." We agree that encouraging a culture of responsibility among investigators is an important goal of human subject protection regulations.
SACHRP proposes the addition to 45 CFR 46 of three sections that would cover, at a minimum: (1) responsibilities of investigators; (2) qualification standards for investigators (e.g., training); and (3) investigator documentation/records.

New regulations to ensure investigator accountability would codify the current ethical expectations for investigators who conduct human subjects research. Regulations addressing investigator responsibility should emphasize the critical role of the investigator and hold the investigator directly accountable for his/her actions. As part of the FWA requirements, institutions are responsible for ensuring that the regulations are effectively applied. The oversight authority (45 CFR Part 46.103(a)) is already in place: "each institution engaged in research … shall provide written assurance … that it will comply with the requirements set forth in this policy."

Adding investigator responsibilities to the HHS regulations would harmonize HHS regulations with those of the FDA and international standards, uniting the regulatory expectations. Models for delineating investigator responsibilities can be found in the drug and device regulations of the FDA (i.e., Subpart D, 21 CFR Part 312 and Subpart E, 21 CFR Part 812) and in internationally accepted guidelines such as the ICH standards (Good Clinical Practice E-6, Section 4) and the CIOMS International Ethical Guidelines For Biomedical Research.

Therefore, SACHRP recommends the following language for inclusion in 45 CFR 46:

§46.102 (Definitions)
Investigator means any individual responsible for the conduct of human subjects research either for the study as a whole or at a particular site.

§46.104 Responsibilities of Investigators.

(a) ***As appropriate to their role in the research, investigators*** *are responsible for ensuring that research is conducted according to:*
  (1) sound research design and scientific methods;
  (2) the IRB approved study plan (protocol);
  (3) the terms of the grant, contract and/or signed funding agreements that are applicable to the investigator;
  ~~*(4) the IRB approved study plan (protocol);*~~
  (4) applicable laws and regulations, including those for protecting the rights, safety, and welfare of human subjects.

(b) Unless exempt from review, investigators are responsible for obtaining initial IRB approval, prior approval for any modifications to the research and, as required, continuing review of the research.

(c) Investigators are responsible for providing the IRB with sufficient information and materials to make the required determinations in §46.111.

(d) Unless waived by the IRB, investigators are responsible for ensuring that informed consent is obtained in accordance with §46.116 ***and as approved by the IRB.*** *Unless waived by the IRB, investigators are responsible for* ***ensuring*** *consent* ***is documented*** *to the extent required by §46.117* ***and as approved by the IRB.***

(e) Investigators are responsible for providing a copy of the informed consent to each subject, unless the requirement of a written consent document is not part of the IRB ***approval.***

(f) When vulnerable populations are involved in research, investigators are responsible for complying with any required additional safeguards.

(g) Investigators are required to permit and facilitate monitoring and auditing, at reasonable times, by the IRB of record, funding ***entities****, sponsors, the Secretary, and other federal and state regulatory agencies, as appropriate.*

(h) In compliance with §46.103(b)(5) of this subpart, investigators shall ensure prompt reporting to the IRB of any noncompliance with the approved protocol or requirements of the IRB, and unanticipated problems involving risks to subjects or others.

(i) Investigators are responsible for personally conducting or supervising the research.

(j) ***Investigators are responsible for ensuring that study staff and trainees are appropriately qualified and trained.***

(k) Investigators are responsible for complying with regulatory and institutional requirements including those relating to financial interests that are relevant to the research.

(l)

§46.105 Qualification Standards for Investigators.

*(a) Investigators must be sufficiently qualified by education, training, and experience that **are** appropriate to their role in the research to assume responsibility for the proper conduct of human subjects research.*

*(b) Investigators **must assure that they** have sufficient time and resources to properly conduct or supervise the research for which they are responsible.*

§46.106 Investigator Records, Reports and Documentation.

*(a) Investigators are responsible for the safe and secure storage of research data (**whether in paper or electronic formats)** and **for adequately** protecting the confidentiality of the data.*

*(b) Investigators are responsible for the accuracy and completeness of **study data.***

(c) Investigators must maintain records appropriate to the research (e.g., the study plan, consent forms, and correspondence from the IRB) and permit inspection of the research records in accordance with §46.104(f).

(d) Investigators must maintain records for at least three years after the research ends or for the length of time specified in applicable regulations or applicable institutional or sponsor requirements, whichever is longer, and should take measures to prevent accidental or premature destruction of these documents.

(e) Investigators must submit written reports to the IRB as requested/required by the IRB.

Attachment C. Consent and Waivers, As Presented

DRAFT RECOMMENDATIONS REGARDING INFORMED CONSENT AND WAIVER OF CONSENT

Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Sebelius:

In accordance with the provisions of the charter for the Secretary's Advisory Committee on Human Research Protections (SACHRP), I respectfully submit for your consideration a recommendation relative to Department of Health and Human Services Regulation for the Protection of Human Subjects as codified in 45 CFR Part 46. This letter represents the xxx in a series of recommendations from SACHRP.

The informed consent requirements found in HHS 45 CFR 46 Regulation for the Protection of Human Subjects in Research provide a bedrock protection for individuals participating in research studies. While the regulatory default for non-exempt research is to obtain and document the informed consent of all participants, the regulations anticipated scenarios where this default requirement would be inappropriate given the proposed methodology, the context in which the research would be conducted and the subject population, and included provisions allowing IRBs to waive some or all elements of informed consent when specific conditions have been met.

In practice, the regulations governing waivers of informed consent at §46.116(d) are constructed in such a way that IRBs have variable understanding of when waivers of selected elements of consent are appropriate. As a result, IRBs have consistently required investigators to include information in consent documents that adds no value to the consent process. In fact, by adding length to consent documents and including irrelevant information it could be argued that the consent process is diminished. In addition, IRBs struggle to interpret how the criteria should be applied in order to grant a full waiver of informed consent.

SACHRP proposes modification of 45 CFR Part 46.116 in order to achieve the following: (1) consolidation of the elements of informed consent at §116 (a) and (b) into one comprehensive list of elements; (2) empower IRBs to waive selected elements of consent when deemed appropriate by the IRB; and (3) clarify the circumstances in which an IRB may grant a complete waiver of informed consent.

The proposed restructuring of 45 CFR Part 46.116 would not erode the bedrock ethical component that is informed consent. Modification of the regulations would instead permit IRBs to more consistently grant partial or complete waivers of informed consent without impinging on the ethical validity of the consent process or the research itself. These waivers are already permitted in the existing regulations, but nuances in the language have deterred IRBs from exercising the flexibility that the regulations were intended to provide.

Therefore, SACHRP recommends the following new language for inclusion in 45 CFR 46:

§46.116 General requirements for informed consent.

In all research involving human subjects, the default standard is that no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (b) or (c) of this section, IRBs shall require that in seeking informed consent the following information shall be provided to each subject when appropriate:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of any appropriate alternative procedures or courses of treatment, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) An explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(9) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(10) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(11) Any additional costs to the subject that may result from participation in the research;

(12) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(13) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(14) The approximate number of subjects involved in the study.

(b) Unless the IRB determines otherwise, informed consent is not required for research involving records or specimens that have been collected for non-research purposes, provided that:

(1) There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data; and

(2) There will be no attempt on the part of investigators to contact subjects for research purposes.

(c) An IRB may waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver has important ethical or scientific justification. For example: (i) scientific validity would be compromised if consent was required because it would introduce bias to the sample selection; or (ii) subjects' behaviors or responses would be biased, such that conclusions would not be meaningful; or (iii) ethical concerns would be raised if consent was required because it would create additional threats to privacy that would otherwise not exist, or there is risk of inflicting psychological, social or other harm by contacting individuals or families.

(3) There is a scientifically and ethically justifiable rationale why the research could not be conducted with another population from whom consent could be obtained.

(4) The research could not reasonably be carried out without the waiver.

(5) The waiver of consent is not justified solely on the basis of convenience, cost, or speed. The waiver should also not be justified because some subjects might decline to participate.

(6) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Attachment D. Consent and Waivers, As Revised

DRAFT RECOMMENDATIONS REGARDING INFORMED CONSENT AND WAIVER OF CONSENT

Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Sebelius:

In accordance with the provisions of the charter for the Secretary's Advisory Committee on Human Research Protections (SACHRP), I respectfully submit for your consideration a recommendation relative to Department of Health and Human Services Regulation for the Protection of Human Subjects as codified in 45 CFR Part 46. This letter represents the xxx in a series of recommendations from SACHRP.

The informed consent requirements found in HHS 45 CFR 46 Regulation for the Protection of Human Subjects in Research provide a bedrock protection for individuals participating in research studies. While the regulatory default for non-exempt research is to obtain and document the informed consent of all participants, the regulations anticipated scenarios where this default requirement would be inappropriate given the proposed methodology, the context in which the research would be conducted **or** the subject population, and included provisions allowing IRBs to waive some or all elements of informed consent when specific conditions have been met.

In practice, the regulations governing waivers of informed consent at §46.116(d) are constructed in such a way that IRBs have variable understanding of when waivers of selected elements of consent are appropriate. As a result, IRBs have **frequently** required investigators to include information in consent documents that adds **little** value to the consent process, **for example, a statement that "the only alternative is not to participate in this research."** In fact, by adding length to consent documents and including irrelevant information it could be argued that the consent process is diminished. In addition, IRBs struggle to interpret **whether and** how the criteria should be applied in order to grant a full waiver of informed consent.

SACHRP proposes modification of 45 CFR Part 46.116 in order to: (1) **consolidate** the elements of informed consent at §116 (a) and (b) into one comprehensive list of elements; (2) empower IRBs to waive selected elements of consent when deemed appropriate by the IRB; and (3) clarify the circumstances in which an IRB may grant a complete waiver of informed consent.

The proposed restructuring of 45 CFR Part 46.116 would not erode the ethical **foundation embodied in** informed consent. Modification of the regulations would instead permit IRBs to more consistently grant partial or complete waivers of informed consent without impinging on the ethical validity of the consent process or the research itself. These waivers are already permitted in the existing regulations, but nuances in the language have deterred IRBs from exercising the flexibility that the regulations were intended to provide.

Therefore, SACHRP recommends the following new language for inclusion in 45 CFR 46:

§46.116 General requirements for informed consent.

Except as provided elsewhere in this policy*, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.*

(a) Basic elements of informed consent. Except as provided in paragraph ***(c) or (d)*** *of this section,* ~~**IRBs shall require that**~~ *in seeking informed consent the following information shall be provided to each subject:* ~~***when appropriate:***~~

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation; ~~***a description of the procedures to be followed, and identification of any procedures which are experimental;***~~

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

~~***A disclosure of any appropriate alternative procedures or courses of treatment, that might be advantageous to the subject;***~~

~~***(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;***~~

~~***(6) An explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;***~~

(4) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights; and

(5) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) ***Optional elements of informed consent. When appropriate, one or more of the following elements of information may also be provided to each subject. In the event an optional element is not to be included, it is not necessary to determine or document that the waiver criteria under paragraph (c) or (d) of this section are met:***

(1) A description of the procedures to be followed, and identification of any procedures which are experimental, and a disclosure of appropriate alternative procedures or courses of treatment, that might be advantageous to the subject;

(2) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(3) A description of any medical treatments that are available if injury occurs, what they consist of, where further information may be obtained, and whom to contact in the event of a research-related injury to the subject;

(4) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
(5) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
(6) Any additional costs to the subject that may result from participation in the research;
(7) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
*(8) A statement that significant new findings developed during the course of the research t**hat** may relate to the subject's willingness to continue participation will be provided to the subject; and*
(9) The approximate number of subjects involved in the study.

~~(b) Unless the IRB determines otherwise, informed consent is not required for research involving records or specimens that have been collected for non-research purposes, provided that:~~

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the basic elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designated to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and
(2) The research could not reasonably be carried out without the waiver or alteration.

(a) An IRB may approve a consent procedure which does not include, or which alters, some or all of the basic elements of informed consent set forth in this section. ~~There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data; and~~
~~(2) There will be no attempt on the part of investigators to contact subjects for research purposes.~~

(c) An IRB may waive the requirements to obtain informed consent provided the IRB finds and documents that:
(1) The research involves no more than minimal risk to the subjects;
~~(2) The waiver has important ethical or scientific justification. For example: (i) scientific validity would be compromised if consent was required because it would introduce bias to the sample selection; or (ii) subjects' behaviors or responses would be biased, such that conclusions would not be meaningful; or (iii) ethical concerns would be raised if consent was required because it would create additional threats to privacy that would otherwise not exist, or there is risk of inflicting psychological, social or other harm by contacting individuals or families.~~
~~(3) There is a scientifically and ethically justifiable rationale why the research could not be conducted with another population from whom consent could be obtained.~~
(2)The research could not reasonably be carried out without the waiver;

~~***(4) The waiver of consent is not justified solely on the basis of convenience, cost, or speed. The waiver should also not be justified because some subjects might decline to participate.***~~

(3) If *appropriate, the subjects will be provided with additional pertinent information after participation.*

(e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

Attachment E. SOH Draft Comments on Local Context

The phrase "local context" does not appear in the federal regulations (45CFR46 or 21CFR56). The concept of "local context" was birthed in guidance. In 1998 the Office for Protection from Research Risks (OPRR - now the Office for Human Research Protection - OHRP) issued internal guidance for OPRR staff on "local context," which stated: "Institutions have a profound responsibility to ensure that all IRBs designated under an OPRR-approved Assurance possess sufficient knowledge of the local research context to satisfy these requirements [45 CFR 46.103(d), 45 CFR 46.107(a)(i-ii), 45 CFR 46.111(a)(3),(a)(4),(a)(7),(b), and 46.116]. This responsibility endures regardless of the IRB's geographic location relative to the institution and the research. It is particularly critical where the research involves greater than minimal risk to subjects or vulnerable categories of subjects." This guidance was updated in 2000 and stands today as current OHRP guidance.

Because of the "local context" guidance, institutions are reluctant to cede authority for IRB review and central IRBs have had to develop burdensome procedures – to the IRBs and to investigators and institutions – for site demographic data and communication, which offer little enhancement to human subject protection.

The 1998 staff memo was written at a time when several universities were turning to independent review boards as a result of adverse actions (e.g., suspension of assurance of compliance) taken by OPRR against these institutions. At that time, there was wide perception by the research community that OPRR did not favor central review, especially if the review was conducted by an independent review board (i.e., "commercial" and/or not institutionally affiliated). This perception was partially tied to the fact that federal assurances were only issued to "institutions," so "independent IRBs" were not eligible for an assurance. This view about the use of independent review boards has changed in recent years at OHRP.

In a correspondence letter dated April 13, 2010, the current Director of OHRP stated: "OHRP is taking steps to address institutions' concerns about relying on an IRB external to the institution. For example, … we have archived prior guidance documents ["Local IRB Review of Multicenter Clinical Trials" [1992] and "Local Institutional Review Board (IRB) Review of Multicenter Clinical Trials Sponsored by the Division of Aids (DAIDS) National institute of Allergy and Infectious Diseases (NIAID)" [1993]] that suggested OHRP favors local IRB review over review by a non-local IRB, a position that OHRP no longer holds. (The reviewing IRB should nonetheless have appropriate knowledge of the local context.)"

Whereas the guidance offered in this response letter supports IRB review by a non-local IRB, it still reinforces the requirement that the reviewing IRB must have special knowledge about the local context and further that the concept of "local context" is essential to the regulatory compliance of the IRB in reviewing research.

FDA has historically supported central review and review by independent review boards. However, in the 2006 FDA guidance (Using a Centralized IRB Review Process in Multicenter Clinical Trials), it states that, "An IRB that is at a different location from the research site can review the research, provided that the IRB is competent to understand the local context of the research. As stated in 21 CFR 56.107(a), this would require sensitivity to community attitudes and the ability to ascertain the

acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice."

Again, while the FDA appears to allow IRBs to have employ a less stringent standard in meeting the requirement for local context (confining it to the IRB membership requirements found in section 56.107), there is still appears to be a new (as of 2006) absolute requirement that the IRB be composed to understand the local context at all sites in which the research would be conducted.

Clearly, both the OHRP and FDA guidance documents are outdated. Many publicly and most privately funded research studies involve multiple sites and support a single IRB that has primary responsibility for review and approval of the research (e.g., an independent review board for industry-sponsored clinical trials, NCI central IRB for NCI-funded trials, or the Partners Healthcare System serving as a central IRB for NINDS-funded research). Because research design and methods must be standardized across sites, and the only flexibility within the protocol is to minimally tailor the consent document, local context takes on less importance in protecting human subjects. IRBs that conduct review for multiple sites collect information about the local setting – local resources, including staffing available to conduct the research, demographic information about the study population, and the consent process – to fulfill the requirement to consider local context. However, the burden of collecting this information might not be justified based on its limited use in protecting research subjects.

Further, even without the recent changes in the research enterprise to more multi-site and collaborative research, the notion that any IRB always has sufficient competence to judge the local context is naïve. In large urban areas where there are hundreds of ethnic groups and languages spoken, an IRB, no matter whether it is located within an institution or is centrally located, will not have the competence to judge local context beyond what is acceptable practice by central or independent review boards.

SOH/SACHRP recommends that OHRP and FDA retire their respective guidance documents and issue guidance, which encourages single IRB review under a "reliance model" that allows an institution to use an external IRB (whether central or independent or other type of single IRB review model) that is deemed competent if its policies and procedures comply with the federal regulations related to IRB composition and review procedures. The use of the term "local context" should be expunged.

Secretary's Advisory Committee on Human Research Protections
July 10-11, 2012
Washington, D.C.

Certification of the Summary of Minutes

I hereby certify that, to the best of my knowledge, the foregoing summary of minutes is accurate and complete.

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Barbara Bierer, M.D., Chair Date